TMC125 (etravirine)

Drug Class: **Non-nucleoside Reverse Transcriptase Inhibitors**

Drug Description

TMC125 is a diarylpyrimidine (DAPY) derivative with potent in vitro activity against HIV. [1]

HIV/AIDS-Related Uses

TMC125, also known as etravirine, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is being investigated for the treatment of HIV. In vitro, TMC125 has equipotent activity against wild-type HIV and NNRTI-resistant variants encoding L100I, K103N, Y181C, Y188L, and G190A/S mutations.[2]

In September 2006, Tibotec opened an expanded access program (EAP) to provide TMC125 to patients in the U.S. who have limited or no treatment options because of virologic failure or intolerance to multiple antiretroviral regimens or who are unable to use currently approved NNRTIs because of resistance or intolerance. The U.S. EAP is part of a larger, international EAP offered by Tibotec. A non-U.S. EAP will be established by Tibotec in Fall 2006.[3]

Pharmacology

TMC125 was designed by Belgian scientists to reduce drug resistance, partly by making a flexible molecule that can fit in the active pocket of HIV's reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations that would defeat other drugs.[4] TMC125 is a highly flexible compound with low in vitro toxicity.[5] TMC125 has garnered attention because of its activity against NNRTI-resistant HIV strains.[6]

A substantial improvement in the relative oral bioavailabililty of TMC125 was achieved with new tablet formulations, compared to tablet formulations used in previous studies. In the TMC125-C170 trial, all 45 HIV uninfected participants received one reference dose of 400 mg TMC125. After a 2-week washout period, participants received one of four test formulations of TMC125. Pharmacokinetics of TMC125 were assessed for 96 hours postdose. Results indicated a marked increase in area under the concentration-time curve (AUC) and serum maximum concentrations (Cmax) for all test formulations compared to the reference dose. Time to maximum concentration (Tmax) and the elimination half-life were similar for all treatments. Less intersubject variability was observed for the test formulations compared to the reference dose. Treatment with TMC125 was generally safe and well tolerated. These new tablet formulations also reduce pill burden.[7]

Several studies of TMC125 in HIV infected people have been promising. In the TMC125-C207 study conducted in London, England, TMC125's effectiveness in HIV infected men with documented efavirenz resistance taking an NNRTI-containing regimen was evaluated. In this open-label, Phase IIa study of 16 HIV infected men with 10- to 500-fold resistance to efavirenz, treatment with TMC125 for 7 days resulted in a median decrease in viral load of slightly less than 10-fold. Seven patients (44%) had a viral load decrease greater than 10-fold. There was no relationship between response to the drug and patient genotype or phenotype.[8] [9]

In the TMC125-C208 trial conducted in the Russian Federation in 2001, a 7-day monotherapy course of TMC125 at a dosage of 900 mg twice daily was given to 12 HIV infected, antiretroviral therapy (ART)-naive patients. The treatment duration was limited to 7 days to prevent the selection of NNRTI-resistant mutants, because a rapid emergence of resistance has been observed for first-generation NNRTIs when given as monotherapy. TMC125-C208's results were compared to the Dutch ERA study that took place between 1997 and 2000, which evaluated the effect of a five-drug, triple-class ART regimen in ART-naive individuals with either primary or chronic HIV-1 infection. Analysis indicated that 1 week of TMC125 monotherapy resulted in a similar decline in viral load compared with 1 week of therapy with a five-drug regimen. The apparent ability of TMC125 to substantially reduce HIV viral load in only 7 days of monotherapy suggests that starting treatment with a TMC125-containing regimen could provide better long-term suppression

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Pharmacology (cont.)

of HIV replication.[10]

In the TMC125-C223 trial, 199 HIV infected patients were randomly assigned to receive an investigator-selected background therapy of TMC125 at either 400 mg or 800 mg twice daily, or a standard-of-care regimen. An interim 24-week analysis suggested TMC125 dosing resulted in HIV viral load log10 reductions of 1.04, 1.18, and 0.19 for patients receiving twice-daily 400 mg TMC125, twice-daily 800 mg TMC125, or standard-of-care, respectively.[11] Week 48 analysis indicated mean HIV viral load log10 reductions of -0.88, 1.01, and -0.14 for the 400 mg, 800 mg, and standard-of-care groups, respectively. At Week 48, TMC125 showed high rates of sustained efficacy in these heavily-pretreated patients. Analysis of response compared to baseline resistance suggests that TMC125 retains activity in the presence of multiple NNRTI mutations where current NNRTIs are not expected to be effective.[12]

Highly treatment-experienced HIV infected patients with drug-resistant HIV may benefit from using TMC125 together with darunavir, a protease inhibitor (PI) approved by the FDA in 2006. Five men started taking twice-daily darunavir 600 mg with ritonavir 100 mg, and twice-daily 200 mg TMC125, with a combination of nucleoside reverse transcriptase inhibitors and/or enfuvirtide. Viral load, CD4 count, and safety parameters were followed from baseline to Week 24; genotypic resistance was assessed at baseline and on the most recent blood sample with detectable viral load. About a month after initiating study treatment, TMC125 coadministered with ritonavir-boosted darunavir were well tolerated. Interim results at Week 4 for the first 4 study participants indicate that viral load decreased and CD4 count increased, with no PI-associated mutations observed by Week 4.[13]

Adverse Events/Toxicity

In clinical trials so far, TMC125 has been safe and well tolerated. Adverse effects have been mild and have included headache and diarrhea.[14] [15]

In the TMC125-C223 trial, approximately 15% of patients receiving TMC125 developed rash, and several of these individuals had to discontinue therapy.[16]

Drug and Food Interactions

Studies have been conducted to determine the drug interactions between TMC125 and ritonavir-boosted tipranavir (TPV/r). In a Phase I open-label, crossover trial that lasted about 5 weeks, 24 HIV uninfected adults received 800 mg TMC125 twice daily for 8 days, then stopped taking TMC125 for a washout period of at least 14 days. After the washout period, participants were randomly assigned to one of two groups. Group 1 took TPV/r 500 mg/200 mg twice daily for several days after the washout period, then added twice-daily 800 mg TMC125 for the rest of the study. After the washout period, Group 2 took twice-daily TPV/r 500 mg/200 mg and twice-daily 800 mg TMC125 for several days, then stopped TMC125 for the rest of the study. Participants took their medications 15 minutes after a meal, and the order of intake was ritonavir, TPV, and TMC125.[17]

When TMC125 was coadministered with TPV/r, exposure to TMC125 (AUC) was decreased by 76%. TPV and ritonavir exposures increased 18% and 23%, respectively, when these drugs were taken concurrently with twice-daily 800 mg TMC125. Given the clinical relevance of these drug interactions, coadministration of TMC125 and TPV/r is not recommended.[18]

In some small studies in healthy volunteers when twice-daily 200 mg TMC125 and twice-daily ritonavir-boosted darunavir (darunavir/r) 600 mg/100 mg are coadministered, changes to darunavir's pharmacokinetics are not clinically relevant. Although TMC125's serum concentration decreased by 37% as compared to twice-daily 100 mg TMC125, the decrease is not considered clinically relevant. However, serum concentration of darunavir/r increases when given with twice-daily 200 mg TMC125 (at a magnitude greater than when given with twice-daily 100 mg TMC125); this suggests that twice-daily 200 mg TMC125 exhibits the best clinical exposure, and current Phase III trials are using this dosing scheme.[19]

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Drug and Food Interactions (cont.)

TMC125 has no clinically relevant effect on the pharmacokinetics or pharmacodynamics of methadone. In a small open-label study, 16 male HIV uninfected volunteers on stable methadone therapy received twice-daily 100 mg TMC125 for 14 days. Safety, tolerability, and symptoms of methadone withdrawal were assessed. No clinically significant withdrawal symptoms were observed and no dose adjustment of methadone was required during coadministration of methadone with TMC125 or during follow-up. Concomitant administration of the two drugs was generally safe and well tolerated.[20]

The bioavailability of TMC125 is not decreased when coadminstered with the H2-antagonist ranitidine or the proton-pump inhibitor omeprazole. The increased exposure of TMC125 when coadminstered with omeprazole is not considered clinically relevant. In a small open-label, 1-crossover study, 19 HIV uninfected volunteers were randomly assigned to receive in 3 periods a single dose of 100 mg TMC125 alone (session 1); 11 days of twice-daily ranitidine 150 mg (session 2); and 11 days of once-daily omeprazole 40 mg (session 3). A single 100 mg TMC125 dose was coadministered on Day 8 of sessions 2 and 3. Sessions were separated by a washout period of 14 days. Ninety-six-hour TMC125 pharmacokinetics were assessed in each session; safety and tolerability were also assessed. Coadministration of a single dose of TMC125 with either ranitidine or omeprazole was generally safe and well tolerated.[21]

Clinical Trials

For information on clinical trials that involve TMC125 (etravirine), visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: TMC125 (etravirine) AND HIV Infections.

Dosing Information

Dosage Form: In clinical trials, 100 and 200 mg capsules of TMC125 have been tested in dosages of 400, 800, and 1200 mg twice daily[22] ; 900 mg twice daily[23] , and 1600 mg twice daily.[24] [25]

New tablet formulations have been developed in an effort to increase AUC and Cmax while reducing pill burden.[26]

Chemistry

CAS Name: Benzonitrile, 4-((6-amino-5-bromo-2-((4-cyanophenyl)amino)-4-pyrimidinyl)oxy) -3,5-dimethyl-[27]

CAS Number: 269055-15-4[28]

Molecular formula: C20-H15-Br-N6-O[29]

C55.18%, H3.48%, Br18.35%, N19.31%, O3.68%[30]

Molecular weight: 435.31[31]

Other Names

TMC 125[32]

R165335[33]

TMC-125[34]

Etravirine[35]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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